Interleukin 2

Contents

Overview

Interleukin 2 (IL-2) is a lymphokine synthesized and secreted primarily by T helper lymphocytes that have been activated by stimulation with certain mitogens or by interaction of the T cell receptor complex with antigen/MHC complexes on the surfaces of antigen-presenting cells (1-5). The response of T helper cells to activation is induction of the expression of IL-2 and receptors for IL-2 and, subsequently, clonal expansion of antigen-specific T cells. At this level IL-2 is an autocrine factor, driving the expansion of the antigen-specific cells. IL-2 also acts as a paracrine factor, influencing the activity of other cells, both within the immune system and outside of it. B cells (6, 7) and natural killer (NK) cells (8-16) respond, when properly activated, to IL-2. The so-called lymphocyte activated killer, or LAK cells (17, 18), appear to be derived from NK cells under the influence of IL-2.

Structural Information

First characterized biochemically from Jurkat cells, a human T cell leukemic line, human IL-2 is a glycoprotein with an apparent molecular weight of 15,000 - 18,000, (19). Natural IL-2 is glycosylated and varying degrees of glycosylation apparently account for the observed range of molecular weights seen on SDS-PAGE. The IL-2 gene was subsequenctly cloned and expressed in eucaryotic cells (19) and *E. coli* (20). Human IL-2 is synthesized as a polypeptide of 153 amino acid residues. The first 20 amino acids represent a signal sequence that is cleaved to produce the mature factor. The mature protein contains three cysteine residues, two of which form a disulfide bond that is required for biological activity (21). Although glycosylation apparently occurs at a single O-glycosylation site on threonine at position three, it is not essential for bioactivity (22). Using probes derived from the human cDNA, a homologous gene was cloned from murine cells (23). Murine IL-2 is approximately 63% identical to human IL-2, but contains a unique stretch of repeated glutamine residues (23). There is marked species cross-reactivity as human IL-2 has been found to be active on murine cell lines. The three- dimensional structure of human IL-2 has been determined using X-ray crystallography and this has shown IL-2 to be an alpha-helical protein with a four-fold core and no beta-sheet structure (24, 25). A recent review (26) provides a structure-function analysis of IL-2, discussing this structure in detail along with information derived from experimentally mutated IL-2 molecules. Cells known to produce IL-2 include thymocytes (27), gamma delta T-cells (28), B-cells (29), CD4+ and CD8+ T-cells (30), and neurons plus astrocytes (15). Recent reviews involving IL-2 and its gene are found in references 5 and 32.

Receptors

The biological activities of IL-2 are mediated through the binding of IL-2 to a multisubunit cellular receptor. Although three distinct transmembrane glycoprotein subunits contribute to the formation of the "definitive" high affinity IL-2 receptor, various combinations of receptor subunits are known to occur (33, 34). Historically, the first receptor subunit identified was the alpha subunit, a 55 kDa, 251 amino acid (aa) residue glycoprotein that contains a very short 13 aa cytoplasmic tail. Although this receptor is specific for IL-2, its affinity is low (Kd = 10 nM) and it apparently has no signal transducing capability (33). Alternative names for this receptor include IL-2R, IL-2R alpha, CD25 and Tac antigen (for activated T-cell) (35). Cells known to express alpha-chains include activated and resting CD4+ and CD8+ T cells (33, 36, 37), resting and activated B cells (38), immature thymocytes (39), endothelium (40), embryonic fibroblasts (41), glioblastoma (oligodendroglial) cells (42), activated monocytes (43), Kupffer cells, macrophages and Langerhans cells (44, 45), and various tumor cells (46). The second subunit to be isolated was the beta subunit, a 70 kDa, 525 aa residue glycoprotein that possesses an extensive 286 aa cytoplasmic region. This region has at least three distinct domains, a serine-rich domain, an acidic (glutamic & aspartic acid) rich domain, and a proline-rich domain. These domains contribute to the signal transducing ability of the beta-subunit that is suggested to involve Jak1, Syk and the src family molecule p56lck (47). The beta-subunit binds IL-2 (Kd = 100 nM) and is involved in the signal transduction mechanims of both IL-2 and the newly discovered IL-15 (33, 48, 49). Cells known to express the beta-chain include activated CD56+ (NK) cells plus CD8+ and CD4+ T cells (36, 37), resting NK cells and, perhaps, CD8+ T cells (36, 37), activated and resting B cells (38), mature thymocytes (39), embryonic fibroblasts (41), resting monocytes (43) and neutrophils (50). The last subunit to be discovered is known as the gamma chain. This is a 64 kDa, 347 aa residue glycoprotein that contains an 86 aa cytoplasmic region. Although no obvious catalytic motif has been identified in this cytoplasmic domain, Jak3 is activated by this molecule (47). In addition, ligand internalization seems to be dependent upon the gamma-chain. Thus, it is suggested that the beta- and gamma-chains may interact through their cytoplasmic domains to transduce an IL-2 signal (33). Unlike the alpha- and beta-chains, the gamma-chain has generally been believed not to bind directly to IL-2. However, there is a recent report that strongly suggests that IL-2 can interact directly with the gamma-subunit (51). The gamma-chain is shared by a number of receptors, including those for IL-4 (type I) (52), IL-7, IL-9 and IL-15 (53) and as a consequence it is alternatively known as the common gamma chain. Finally, cells known to express the gamma-chain

include monocytes (54, 55), neutrophils (56), thymocytes (57), CD4+ and CD8+ T cells, NK cells and B cells (53).

The existence of three distinct subunits allows for multiple subunit combinations. The alpha-beta-gamma heterotrimer is generally considered to be the high affinity (Kd = 10 pM), signal transducing receptor for IL-2 (33). Cells known to express this combination of subunits include activated T cells (58) and monocytes (43). In humans, a second high affinity dimeric beta-gamma subunit combination (Kd = 1 nM) is also known to transduce a signal (33). Cells believed to express this functional combination of subunits include NK cells (51, 57), neutrophils (50, 56), monocytes (43) and CD8+ T cells (36). Although the alpha-beta subunit combination is generally not believed to transduce a signal (Kd = 100 pM), studies with embryonic fibroblasts showing an apparent absence of gamma-subunits still show physiologic responsiveness (33, 59). The alpha-gamma subunit combination has no reported activity. The reported Kds for the various subunit combinations reflect the contributions of individual subunit ligand-association/ dissociation rates.

Soluble forms of many cytokine receptors have been reported in recent years, and a soluble form of IL-2R alpha appears in serum, concomitant with its increased expression on cells (60-62) Its function is unclear, since it would be expected to be a poor inhibitor of IL-2 activity because of its low affinity for IL-2. In any case, the soluble IL-2R alpha is an indicator of T cell activation, and may predict the onset of transplant rejection, among other things (62) There are reports of soluble form of IL-2R beta, as well (63, 64). Recent reviews covering the IL-2 receptor complex can be found in references 33, 34, 44, 53.

Biological Activity:

As previously discussed, IL-2 is a factor produced and secreted primarily by activated T helper cells that acts as a paracrine factor driving the expansion of antigen- specific cells and as a paracrine factor influencing the activity of a number of other cells including B cells, NK cells and LAK cells. A simplified but useful view of these activities is of lymphocytes expanding under the influence of IL-2 and becoming the target of other cytokines that cause their functional differentiation (65). Whether IL-2 is itself a differentiation factor in these systems is the subject of much interest and debate.

With respect to the specific role of IL-2 on the differentiation of T cells, the separation of CD4+ T helper cells into the categories TH1 and TH2 according to their function in cell mediated or humoral immunity is a concept that is proving useful (66). In this system each category of cells secretes a characteristic set of cytokines that functions as a network to push the system either towards cellular immunity (delayed type hyper-sensitivity and cellular cytotoxicity), associated with TH1; or towards humoral immunity (antibody-mediated), associated with TH2. IL-2, along with IFN-gamma and TNF-beta, is a defining product of the TH1 subset. Although the TH1 and TH2 subsets are relatively clearly defined in the murine immune system, these categories are not so clear- cut in the human immune system where the designations TH1-like and TH2-like have been suggested.

Other cells under the possible influence of IL-2 are neutrophils (50, 67), monocytes (43), and gamma delta T cells (68), all of which demonstrate either activation, augmented function, or increased survival when exposed to IL-2. Finally, it should be mentioned that IL-2 is finding its way, along with many other cytokines, into the neurosciences as a possible neuromodulator (31, 69, 70) and growth regulator of glial cells (71). It has also been reported that a transglutaminase can dimerize IL-2, allowing the regeneration of axons in rat optic nerves (72, 73). The dimerized IL-2 is toxic to oligodendrocytes that would otherwise inhibit axon outgrowth. It is not yet clear what oligodendroglial receptors or IL-2 receptor subunit combination might be involved.

Clinical Interest

Because of the central role of the IL-2/IL-2R system in mediation of the immune response, it is obvious that monitoring and manipulation of this system has important diagnostic and therapeutic implications. IL-2 has shown promise as an anti- cancer drug by virtue of its ability to stimulate the proliferation and activities of tumor-attacking LAK and TIL (tumor-infiltrating lymphocytes) cells (74-77). However, problems with IL-2 toxicity are still of concern and merit investigation (78). The basic biology of these strategies in cancer, infectious disease and transplantation has been recently reviewed.(79, 80). The monitoring of increased serum levels of IL-2 and soluble IL-2 receptor (a naturally occurring portion of the IL-2R alpha chain), shows promise as a predictor of the onset of rejection episodes in allograft recipients (81). Antibodies against IL-2 or IL-2 receptors may have potential in the prevention of allograft rejection and suppression of autoimmune diseases (82, 83).

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